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Review

Plastid-to-nucleus communication, signals controlling the running of the plant cell ☆

Juan de Dios Barajas-López, Nicolás E. Blanco, Åsa Strand *

Umeå Plant Science Centre, Department of Plant Physiology, Umeå University, S-901 87 Umeå, Sweden

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ABSTRACT

The presence of genes encoding organellar proteins in both the nucleus and the organelle necessitates tight coordination of expression by the different genomes, and this has led to the evolution of sophisticated intracellular signaling networks. Organelle-to-nucleus signaling, or retrograde control, coordinates the expression of nuclear genes encoding organellar proteins with the metabolic and developmental state of the organelle. Complex networks of retrograde signals orchestrate major changes in nuclear gene expression and coordinate cellular activities and assist the cell during plant development and stress responses. It has become clear that, even though the chloroplast depends on the nucleus for its function, plastid signals play important roles in an array of different cellular processes vital to the plant. Hence, the chloroplast exerts significant control over the running of the cell. This article is part of a Special Issue entitled: Protein Import and Quality Control in Mitochondria and Plastids.

1. Introduction

Chloroplasts, like mitochondria, evolved from free-living prokaryotic organisms that entered the eukaryotic cell through endosymbiosis. The gradual conversion from endosymbiont to organelle during the course of evolution has been accompanied by a dramatic reduction in genome size as the chloroplasts lost most of their genes to the nucleus and the endosymbionts became dependent on their eukaryotic host. The plastid genomes of current land plants encode 75 to 80 proteins [1] whereas the number of proteins in the chloroplast is estimated to be between 3500 and 4000 proteins [2]. Thus, the majority of the plastid proteins are encoded in the nucleus. The presence of genes encoding plastid proteins in both the nuclear and the plastid genomes presents the complex problem to the plant cell to coordinate the activities of the these different genomes [3–5]. In the photosynthetic electron transport complexes of the thylakoid membrane, the core subunits are encoded by the chloroplast genome and the peripheral subunits are encoded by the nuclear genome. In the stroma, the large subunit of Rubisco is encoded in the plastids whereas the small subunit is nuclear encoded. To ensure that all these photosynthetic complexes are assembled stoichiometrically, and to enable their rapid reorganization in response to changes in the environment, the process of so called retrograde signaling has evolved where plastids emit signals that regulate nuclear gene expression to match the status of the plastids [6–9].

The first evidence of the existence of a "plastid signal" came from studies of mutants with morphologically aberrant plastids. These include mutants with defective plastid protein synthesis such as the plastid ribosome-deficient *albostrians* barley mutant and the *Brassica napus al* mutant [10–12]. These mutants demonstrated reduced expression of nuclear genes encoding plastid components suggesting that a plastid signal was emitted to repress the nuclear encoded photosynthesis genes [12]. These results opened the research field to investigate how different plastid processes trigger signals that modulate nuclear gene expression [6]. We now know that several different plastid processes produce signals that regulate specific sets of genes or regulons and several molecular candidates for plastid signals have been described. Plastid signals and communication between the plastids and nucleus is of particular importance during plant stress responses. For plants to respond optimally to environmental stresses it is necessary that the cytosolic and plastid signaling networks are integrated to produce a coordinated response in the different cellular compartments [13]. Plastid signals also coordinate cell cycle and coupling of DNA replication in the cell and play a major role during chloroplast development [14,15]. Furthermore, it was recently demonstrated that organelle-to-nucleus communication also plays a role in intercellular communication via plasmodesmata [16] and that plastid signals are key factors driving the transition from cell proliferation to cell expansion [17]. Thus, it is clear that plastid signals play important roles in an array of different cellular processes of the plant.

Plastid signals are essential to the plant both during the initial developmental stages (biogenic control) and in adult stage to face

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* Corresponding author. Tel.: +46 90 786 9314; fax: +46 90 786 6676.
E-mail address: Asa.Strand@plantphys.umu.se (Å. Strand).

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changes in the environment (operational control) [18]. However, the tentative plastid signals identified to date can be linked primarily to specific stress conditions. The photosynthetic reactions housed in the chloroplasts are extremely sensitive to stress and the chloroplasts could therefore play a critical role as sensors of changes in the growth environment [13,19]. This review will focus on two different types of plastid signals influencing nuclear gene expression during different stress conditions; 1) metabolites as plastid signaling molecules, tetrapyrroles and the recently discovered phosphonucleotide 3′-phosphoadenosine 5′-phosphate (PAP) and 2) signals related to photosynthetic electron transport such as changes of the redox state of the chloroplast and accumulation of the reactive oxygen species, singlet O_2 and H_2O_2. Plastid signaling has also been associated with the organellar transcriptional and translational activity (PGE) involving GUN1 in particular [14,20,21] and to the carotenoid biosynthesis [22]. Due to space limitations these aspects will not be covered in this review.

2. Metabolites as plastid signaling molecules

2.1. The putative role of tetrapyrroles in plastid signaling

Higher plants synthesize four major tetrapyrrole molecules via a common branched pathway in the plastids: chlorophyll, heme, siroheme and phytochromobilin. Many tetrapyrroles are excited by light and if left unquenched they can form highly toxic radicals. Tetrapyrrole synthesis is therefore tightly regulated to prevent the accumulation of intermediates that may endanger the plant cell. Perturbations in the tetrapyrrole pathway have been shown to affect expression of photosynthesis-associated nuclear genes (*PhANGs*) in both green algae and higher plants [23–31]. Mutants with impaired communication between the chloroplast and the nucleus referred to as the genome *un*coupled, or *gun* mutants were isolated from genetic screens [7,32]. The *gun1–6* mutants express *PhANGs* when exposed to oxidative stress whereas wild type demonstrates strong suppression of photosynthetic gene expression under the same conditions [7,32]. Five of the six GUN genes, *GUN2–6*, encode components closely associated with tetrapyrrole biosynthesis and the respective mutants have impaired flux through the tetrapyrrole biosynthesis pathway. GUN1 on the other hand, is a chloroplast localized pentatricopeptide-repeat (PPR) containing protein with unknown function. Thus, the *gun* mutants provided strong evidence for the involvement of tetrapyrroles in communication between the chloroplast and the nucleus in plants.

Environmental changes affect flux through the tetrapyrrole biosynthesis causing perturbations and the accumulation of specific metabolites. Thus, flux through tetrapyrrole biosynthesis could act as an indicator of changes in the environment and the signals triggered by flux perturbations are therefore important during stress responses but they also play roles during seedling and chloroplast development [25,32,33]. Heme and Mg-ProtoIX affect expression of *PhANGs* and in the *gun5* mutant expression of genes encoding proteins involved in the light harvesting and electron transport reactions of photosynthesis, enzymes in metabolic pathways such as the Calvin cycle and tetrapyrrole biosynthesis, and proteins involved in translation of chloroplastic-encoded genes is mis-regulated following exposure to oxidative stress [25]. In addition, Mg-ProtoIX has been shown to coordinate cell cycle and coupling of organellar and nuclear DNA replication in red alga and tobacco BY-2 cells [15]. In red algae Mg-ProtoIX was shown to mediate a proteasome-dependent protein degradation by binding to and inhibiting a SCF-type E3 ubiquitin ligase (FBX3). Inhibition of FBX3 results in release of Cyclin 1 and activation of CDKA, stimulating nuclear DNA replication [34]. Furthermore, in non-photosynthetic plastids of BTY2 tobacco cells, tetrapyrroles were shown to play a role in amyloplast differentiation and regulation of the nuclear encoded starch biosynthesis genes ADP-Glucose Pyrophophorylase (AGpS) and the Granule-Bound Starch Synthase (GBSS) [35]. Thus, the collected data suggests that tetrapyrroles play important regulatory roles in diverse cellular processes in plants and algae.

2.1.1. Chlorophyll intermediates putative plastid signals during oxidative stress

Over 20 years ago Mg-ProtoIX and its methyl ester Mg-ProtoIX-ME were suggested to act as plastid signals regulating nuclear encoded genes associated with photosynthesis. This proposal was based upon studies demonstrating that accumulation of these chlorophyll intermediates coincided with changes in nuclear gene expression [29,30,36,37]. This model was later supported by the characterization of the *gun5* mutant. The *gun5* mutant has a lesion in the H-subunit of Mg-chelatase that catalyzes the first reaction in the "chlorophyll branch" of tetrapyrrole biosynthesis and has impaired flux through the tetrapyrrole biosynthetic pathway [38]. The *gun5* mutant demonstrates a mis-regulation of a large number of *PhANGs* when exposed to oxidative stress [25] and in contrast to wild type, *gun5* did not demonstrate significant accumulation of Mg-ProtoIX following exposure to oxidative stress [25]. To induce oxidative stress and to trigger the GUN5 signal, seedlings are commonly grown on norflurazon. Norflurazon inhibits phytoene desaturase (PDS) in the carotenoid biosynthetic pathway. The photooxidation caused by norflurazon treatment is limited to the plastid and results in complete destruction of the thylakoid membrane [39,40]. However, norflurazon treatment generates an artificial condition of severe stress where specific responses of the plant may be difficult to reproduce due to pleiotropic effects caused by the treatment [41–43]. The role of Mg-ProtoIX/Mg-ProtoIX-ME as a plastid signal was subsequently questioned when reported accumulation of Mg-ProtoIX following norflurazon treatment was not observed in two different studies [42,43]. Consequently, no correlation between *LHCB* expression and Mg-ProtoIX amounts could be reported in those studies. While the source of the GUN5 dependent plastid signal induced by oxidative stress was still believed to be linked to tetrapyrrole biosynthesis, the exact nature of the signal was challenged. It was suggested that either rapid changes in the flux through the tetrapyrrole pathway, ROS accumulation, activity of Mg-chelatase or accumulation of Mg-ProtoIX in a specific cellular compartment could be the origin of the plastid signal [42,43].

The contradictory results and the controversy regarding the signaling role for Mg-ProtoIX have stimulated the field to make efforts to elucidate the mechanisms involved in the tetrapyrrole-mediated signal. Arabidopsis mutants affected in the I-subunit of the Mg-chelatase, *cs* and *chl42* mutants did not demonstrate a gun phenotype following exposure to oxidative stress [38] . This was an unexpected result and provided support for a specific function for the H-subunit (GUN5) of the Mg-chelatase complex in plastid signaling. It was previously suggested that CHLH monitors porphyrin levels by binding excess ProtoIX and/or Mg-ProtoIX, sending a negative signal or inhibiting a positive signal to the nucleus via a hypothetical downstream factor(s) [38]. However, it was subsequently shown in Arabidopsis that there are two genes encoding I-subunits of Mg-chelatase, CHLI1 and CHLI2 [44]. When the double mutant, *chli1chli2,* was generated, the double mutant did indeed demonstrate a gun phenotype [45], suggesting that the signal is not dependent on CHLH but is linked to the tetrapyrroles.

It was also suggested that ROS accumulation was the origin of the GUN5/tetrapyrrole mediated plastid signal instead of the specific accumulation of Mg-ProtoIX/Mg-ProtoIX-ME [42,43]. The conditions used to trigger the GUN5 mediated plastid signal results in oxidative stress and accumulation of ROS. The different ROS species activate distinct signaling pathways [13] and the release of ROS could be an alternative explanation for the role of tetrapyrrole intermediates in retrograde signaling because many porphyrins are photoreactive and generate $^1O_2$ in the presence of light [46]. However, specific ROS eliminators were shown to only partly reverse the norflurazon-triggered repression of *LHCB*

[23]. In a different study, the expression of marker genes for ROS was investigated in the *gun5* mutant and the expression of those genes were not different in *gun5* compared to wild type and it was concluded that the *gun5* phenotype is not related to an altered accumulation of ROS [41].

The variability in the amounts of tetrapyrroles detected in different reports [25,42,43] could possibly be explained by differences in the sampling of the plant material. Accumulation of Mg-ProtoIX/Mg-ProtoIX-ME following exposure to oxidative stress was shown to be rapid and transient [23,33]. Following short term (<96 h) norflurazon treatment a large accumulation of Mg-ProtoIX was observed and accompanying *LHCB* repression [23]. However, long term (more than 6 days) exposure to norflurazon resulted in a decline of the accumulated pools in these experiments [23]. A more controlled way to expose seedlings to oxidative stress is to use methyl viologen (MV), an inhibitor of photosynthetic electron transport which catalyses the monoelectronic photoreduction of O_2 to generate superoxide ($O_2^{\bullet -}$) and H_2O_2. Following exposure to MV the levels of Mg-ProtoIX and Mg-ProtoIX-ME increased gradually with the highest amounts observed following 3 h exposure and already after 4 h exposure to MV, the accumulated Mg-ProtoIX/Mg-ProtoIX-ME declined towards control levels [33]. This transient nature of the stress-induced accumulation of tetrapyrroles could explain the variability in the amounts of tetrapyrroles detected in different reports [25,42,43]. The fact that tetrapyrrole accumulation is transient following stress exposure is not surprising, given that accumulation of free chlorophyll intermediates have deleterious effects on cellular function and when tetrapyrroles accumulate in the cell for prolonged periods, plants suffer severely from photodynamic damage [47–50]. In summary, Mg-ProtoIX and Mg-ProtoIX-ME have been shown to accumulate when plants and algae are exposed to factors that give rise to oxidative stress such as exposure to low temperatures and inhibitors photosynthetic electron transport [23,25,33,51–54]. The reason for this rapid accumulation could be explained by the fact that the aerobic cyclase reaction was shown, both in Arabidopsis and cucumber, to be extremely sensitive to oxidative stress [54,55]. Thus, impaired flux through chlorophyll biosynthesis and the accumulation of Mg-ProtoIX/Mg-ProtoIX-ME is an indicator of changes in the environment and results in changes in *PhANG* expression [33,52]. Whether accumulation of Mg-ProtoIX is itself an important part of the tetrapyrrole-mediated signal remains unclear.

The genes encoding the components involved in chlorophyll biosynthesis including the subunits of the Mg-chelatase are regulated by the transcription factors Golden 2-like1 and 2 (GLK1/2). Furthermore, GLK transcription factors are functionally conserved within the plant kingdom and required for chloroplast development as demonstrated by the *glk1glk2* double mutants that are pale green and deficient in the formation of the photosynthetic apparatus [56,57]. Interestingly, *PhANG* expression was shown to be less responsive to norflurazon treatment in the *glk1glk2* double mutant in Arabidopsis compared to wild type suggesting that *glk1glk2* exhibit a weak gun phenotype. The phenotype was consistent with reduced levels of chlorophyll intermediates in the *glk1glk2* mutant supporting a role for perturbed tetrapyrrole pools in plastid signaling [58]. However, the *PhANG* expression was significantly suppressed in *glk1glk2* compared to wild type under control conditions making the results difficult to interpret. The two *GLK* genes respond to plastid retrograde signals [58]. Thus, the GLK genes are sensitive to feedback signaling from the chloroplast and it is possible that they operate downstream of plastid retrograde signaling in more long-term acclimatory responses [58].

To act as signaling molecule and to affect the activity of cytosolic or nuclear signaling components such as the GLKs, the chlorophyll intermediate must reach the cytosol. Numerous porphyrins synthesized in the chloroplast, e.g. chlorophyll catabolites, heme and heme precursors have been found to exit the chloroplast [53,59–61]. A method was developed by two independent laboratories [53,62] using single photon laser excitation in combination with confocal scanning microscopy to detect tetrapyrroles *in vivo*. By using this method and by HPLC quantification of fractionated cells Mg-ProtoIX/Mg-ProtoIX-ME was detected in the cytosol during stress conditions and it was proposed that the tetrapyrroles are transported across the membrane acting as putative signaling metabolites [23,53]. However, the route(s) for transport of any tetrapyrroles from the chloroplast or the components involved in the transport are still unknown. In order to investigate whether accumulation of Mg-ProtoIX is itself an important part of the tetrapyrrole-mediated signal, cytosolic ligands of Mg-ProtoIX were isolated from a proteomic study [52] and interactions between Mg-ProtoIX and a large number of proteins associated with oxidative stress responses were identified, consistent with the observed accumulation of Mg-ProtoIX and Mg-ProtoIX-ME under those conditions [23,25,33,51–54]. In addition, a regulatory system, including HSP90 proteins and the transcription factor HY5, that is modified by tetrapyrroles in response to oxidative stress was suggested [33] (Fig. 1). This is analogous to the regulatory HSP70-HSP90-HAP1 complex in yeast that responds to heme accumulation and controls the oxidative response [63,64]. Similar to the accumulation of Mg-ProtoIX/Mg-ProtoIX-ME in plants, heme accumulation in yeast is an indicator of changes in the environment and heme acts as a molecular switch between anaerobic and aerobic growth. Tetrapyrrole binding was shown to inhibit the HSP90 ATPase activity [33] and in addition, the specific gun phenotype was strongly reduced in *gun5-HSP90RNAi* plants suggesting that HSP90 proteins respond to the GUN5 signal and that HSP90 proteins are required for *PhANG* expression in the *gun5* mutant under stress conditions. In addition, the *hy5* mutant demonstrated a gun phenotype when exposed to oxidative stress suggesting that HY5 acts downstream of the GUN5 signal [33]. Furthermore, the *hy5* mutant was also insensitive to the treatment with the inhibitor of HSP90, geldanamycin (GDA) supporting the link between HY5 and HSP90 (Fig. 1). Thus, HSP90 and HY5 have been identified as two additional components in the GUN5 pathway and further analysis of the GUN5–HSP90–HY5 pathway will elucidate the mechanism involved in the regulation of *PhANGs* in response to perturbations of the tetrapyrrole biosynthesis. Although the role of Mg-ProtoIX as a signaling component has been challenged no alternative model has so far been supported by data and there may yet be a role for Mg-ProtoIX in regulating nuclear gene expression in, for example, responses to ROS and other stresses [65,66].

2.1.2. Heme, a tentative signal inducing PhANG expression during seedling development

Accumulation of the tetrapyrrole heme regulates gene expression in animal and yeast cells [64,67–69]. Similarly, in *Chlamydomonas reinhardtii*, feeding of heme to cultures in the dark activated expression of *HSP70A* whereas ProtoporphyrinIX and Protochlorophyllide had no effect [24,29]. The induction *HSP70A* expression was mediated by the same plastid response element (PRE) in the *HSP70A* promoter that has been shown to mediate induction by Mg-ProtoIX and light. In an extensive study of the expression profiles following feeding with heme and Mg-ProtoIX it was demonstrated that feeding with tetrapyrroles triggered global changes in the gene expression and almost 1000 genes changed their expression level significantly upon feeding of Mg-ProtoIX or heme [70].

A new Arabidopsis gain-of-function mutant, *gun6-1D*, with a phenotype similar to the *gun2–gun5* mutants with high *PhANG* expression compared to wild type when grown on norflurazon has recently been reported [32]. In the *gun6-1D* mutant, a T-DNA insertion 8 kb from the gene encoding the plastid ferrochelatase 1 (FC1, heme synthase) cause a 3-fold increase in both *FC1* expression and in total plastid ferrochelatase activity [32]. Interestingly, over-expression of the second plastid ferrochelatase, FC2 failed to increase *PhANG* expression. Thus, in contrast to the FC1 OX lines, the FC2 OX lines did not exhibit a gun

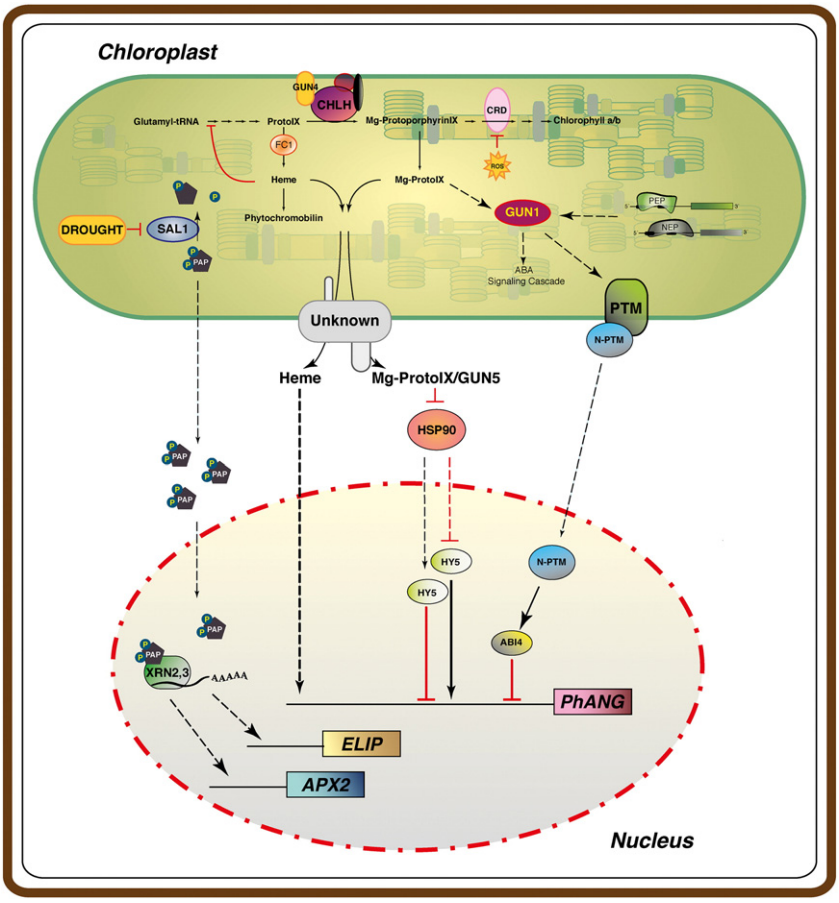

Fig. 1. Metabolites as plastid signaling molecules. Heme and Mg-ProtoIX have been suggested to regulate nuclear gene expression. Heme acts as a positive regulator of *PhANGs* although the exact mechanism in which this compound reaches the nucleus or the different components that mediate the signal to the nucleus are unknown. Mg-ProtoIX accumulates under oxidative stress due the high sensitivity to ROS of the cyclase complex. Interaction between Mg-ProtoIX and HSP90 inactivates the ATPase activity of HSP90 resulting in a HY5 dependent repression of *PhANG* expression. Plant stress triggered by drought or high light inhibits the activity of SAL1 promoting accumulation of PAP in the chloroplast. PAP blocks XNR2 and XNR3 activities and thereby induces gene expression associated with stress response mechanisms. PTM is a general stress sensor in the outer envelope membrane of the chloroplast. A GUN1-mediated response activates a proteolytic mechanism where the N-terminal part of the protein N-PTM is released. The PTM peptide is able to travel to the nucleus to modulate nuclear gene expression by inducing the ABI4 transcription factor.

phenotype when grown on norflurazon. It may be that the FC2 branch is inactive in the norflurazon-treated plastids or that the FC2-produced heme is allocated differently within the plastids [32]. Even though both FC1 and FC2 are localized to the plastid, their sequences and expression profiles suggest functional differences [71–73]. FC2 contains a regulatory hydrophobic C-terminal LHC motif associated with light harvesting complexes [74]. Genetic and biochemical experiments presented by Woodson et al. [32] suggest that increased flux through the heme branch of the plastid tetrapyrrole biosynthetic pathway increases *PhANG* expression. These authors proposed a model where healthy plastids emit heme produced specifically by the FC1 enzyme as a positive signal. This signal controls *PhANG* expression and in the absence of this signal, the plant cannot sustain normal growth responses [32].

Surprisingly, the *gun6-1D* mutant did not show a significant increase in heme levels compared to wild type. It was suggested that FC1 contributes to a specific pool of heme that may be used as a retrograde signal and that is responsible for the regulation of *PhANG* expression (Fig. 1). The synthesis of tetrapyrroles is complex and the pathway is regulated at multiple levels and involves separate pools of products. Accumulation the tetrapyrrole Mg-ProtoIX/Mg-ProtoIX-ME has been shown to be rapid and transient [23,33] and this could also be the case for heme. Furthermore, it has been suggested that accumulation of tetrapyrroles in a specific cellular compartment is the source of the plastid signal [43]. It is also possible that damaged plastids in the *gun6-1D* mutant accumulate less Mg-ProtoIX compared to wild type. Increased FC1 activity would reduce Mg-ProtoIX levels by reducing the ProtoIX availability. Furthermore, an alternative explanation for the *gun5* phenotype under oxidative stress could also be an increased heme content in the *gun5* mutant. Detailed analysis of the tetrapyrrole levels in these different genetic backgrounds under different growth conditions will reveal the exact mode of signaling involved in the tetrapyrrole mediated pathway.

To play a signaling role heme and/or Mg-ProtoIX must be emitted from the plastids but like Mg-ProtoIX, heme is cytotoxic in an unbound state. In Arabidopsis, a tryptophan-rich sensory protein (TSPO) was shown to play a role in porphyrin binding and scavenging during plants stress [75]. It was also recently shown that TSPO binds heme *in vitro* and *in vivo,* and the membrane associated TSPO may therefore play a role in heme trafficking and signaling during plastid development. In support of this, it was shown that TSPO from the photosynthetic bacterium *Rhodobacter sphaeroides* is involved in the regulation of photosynthetic gene expression and that this function of TSPO may be related to the efflux of specific porphyrins that are intermediates in photopigment biosynthesis [76].

2.2. Phosphoadenosine phosphate, a signaling metabolite involved in drought response

A novel retrograde signaling role was recently assigned to phosphonucleotide 3′-phosphoadenosine 5′-phosphate or PAP [77]. PAP accumulates in the chloroplast under drought or exposure to excess light and functions as a mobile signal that alters RNA metabolism by

inhibiting exoribonucleases. PAP was shown to be essential for the induction of stress-induced genes such as *APX2* and *ELIP2* [77].

The role of PAP as a signaling metabolite was discovered from the characterization of mutants with altered expression of *APX2*. The altered *APX2* expression 8 (*alx8*) mutant was identified in a screen for mutants with impaired regulation of *APX2* [78,79]. The *alx8* mutant exhibits constitutive upregulation of *APX2* along with constitutive upregulation of as much as 25% of the HL-regulated transcriptome compared to wild type. In addition, those transcripts show hyperexpression upon exposure to high light [78,79]. Furthermore, 70% of the genes induced in response to excess light are also upregulated by drought [80]. Consequently, the *alx8* mutant was found to be drought tolerant, thus, surviving water deprivation significantly better than wild-type plants [77]. The *alx8* mutant has a lesion in the SAL1/ALX8/FRY1 gene [79,81]. SAL1 is a phosphatase that hydrolyzes a phosphate group from both phosphonucleotides and inositol polyphosphates *in vitro* [82,83]. The phosphonucleotide 3′-phosphoadenosine 5′-phosphate or PAP is produced from PAPS during sulphation reactions catalyzed by sulfotransferases [84]. SAL1 dephosphorylates PAP to AMP and in this way regulates the amount of PAP in the plant cell. PAP accumulated 20-fold in the *alx8* mutant compared to wild-type plants, which is similar to the 30-fold increase in PAP seen in wild type when exposed to drought and HL [77].

SAL1 was conclusively demonstrated to be localized to the chloroplast and mitochondria using three different methods; full-length SAL1 fused to GFP at the C-terminus accumulated in both chloroplasts and mitochondria of transiently transformed Arabidopsis cells, stable transgenic lines with SAL1:GFP fusion protein showed SAL1 in both organelles, and cellular fractionation also demonstrated SAL1 localization in the mitochondria and the chloroplast. It is possible that the activity of SAL1 in the chloroplast is inhibited by stresses such as drought and excess light, resulting in an accumulation of PAP triggering changes in nuclear gene expression as demonstrated by the changed expression of *ELIP2* and *APX2* in the *alx8* mutant (Fig. 1). Although other plastid signals are triggered by stress e.g. tetrapyrrole mediated signal(s) or the signal triggered by inhibitors of plastid translation, there is little overlap between the PAP dependent transcriptome and other plastid signal triggered transcriptomes suggesting that the signal triggered by PAP is specific.

PAP was shown in yeast to inhibit the activity of the exoribonucleases (XRNs) and in this way alter RNA catabolism [85]. In Arabidopsis, the XRN gene family has three members: XRN2, XRN3 and XRN4. XRN2 and XRN3 are orthologs of the yeast Xrn2p/Rat1p and are localized to the nucleus whereas XRN4 is cytosolic and a functional ortholog of the yeast Xrn1p [86]. Excised hairpin loops that form part of precursor miRNA transcripts have been identified as substrates of XRN2 and XRN3. Transcripts for 19 genes that are confirmed targets of miRNAs were increased by at least threefold in the *alx8* mutant compared to wild type suggesting that XRN2/XRN3-regulated genes respond to PAP accumulation. Furthermore, the drought tolerance, molecular and morphological phenotypes of the *xrn2xrn3* double mutant and the *alx8* mutant are similar suggesting that PAP accumulation can also inhibit XRN function in plants [85] (Fig. 1).

To reach the nucleus and inhibit the XRNs PAP must exit the chloroplast and enter the nucleus. In support of this, it was demonstrated that SAL1 targeted to the nucleus fully complemented the *alx8/sal1* mutant phenotypes, including total leaf PAP levels, gene expression and drought tolerance. This suggests that PAP can move between cellular compartments. Two potential mechanisms for the SAL1-PAP-XRN pathway are suggested by the authors, first, XRNs may alter mRNA levels by altering small and/or cleaved RNA pools or, alternatively, XRNs alter gene transcription by affecting transcription termination [77]. To elucidate the underlying gene regulatory mechanisms triggered by the SAL1-PAP-XRN pathway and to indentify the substrates for the nuclear XRNs are exciting tasks for the future.

3. Plastid signals related to photosynthetic electron transport activity

Changes in chloroplast homeostasis are closely associated with changes in photosynthetic activity and increases in the levels of reactive oxygen species (ROS). Changes in the redox status of the photosynthetic electron transport chain (PETC) trigger retrograde signaling processes. The signals linked to photosynthetic electron transport activity are responsible for the well-coordinated expression of photosynthesis genes encoded in both the plastids and the nucleus. Furthermore, these signals are important for the proper handling of incoming light energy during the greening process of young seedlings and for adult plants to acclimate to adverse growth conditions. There are at least three different retrograde signals related to photosynthesis 1) accumulation of $^1O_2$ 2) an exacerbated production of the $O_2^{\bullet -}$ and accumulation of its more stable product H_2O_2 3) an overreduced plastoquinone pool and/or a change in the redox status of the acceptor or donor side of PSI.

Given the nature of the photosynthetic process it is difficult to address ROS- and the redox-mediated retrograde signaling pathways as independent autonomous pathways since most likely their modes of action are interconnected. Thus, the retrograde signals triggered by changes in the photosynthetic electron transport activity should be evaluated as a network sensitive to different factors, environmental and developmental, that modulate the intensity and quality of the message from the plastids to the nucleus. With this in mind, the following two sections will present the ROS and the redox based retrograde signaling pathways operating both during early developmental stages (biogenic) and in the adult stage to face changing environmental conditions (operational control) [18].

3.1. ROS, a cocktail of singlet O_2 and H_2O_2

At high irradiances, and other stress conditions that affect photosynthetic electron transport rate, the equilibrium between production and scavenging of ROS is perturbed, resulting in a transient increase in ROS levels [87]. The ROS generated in chloroplasts are singlet oxygen ($^1O_2$) by PSII and the superoxide anion ($O_2^{\bullet -}$) formed at PSI due to an over-reduction of electron carriers, leading to the reduction of oxygen (the Mehler reaction). The accumulating $O_2^{\bullet -}$ is metabolized to H_2O_2 [88,89]. The damaging effects of ROS are oxidation of lipids, proteins and enzymes necessary for the proper function of the chloroplast and the cell as a whole [90]. Plants have developed several strategies to protect themselves against excess ROS. Carotenoids, tocopherols, glutathione and ascorbate are all ROS scavengers [91]. ROS converting enzymes such as superoxide dismutase (SOD), ascorbate peroxidase (APX), catalase (CAT), glutathione peroxidases (GPX), and peroxiredoxin (PrxR) that can dismutate O_2 radicals and scavenge H_2O_2 play an important role as ROS defense mechanisms [91,92]. Although the different forms of ROS cause similar cellular damage [93], the different ROS activate distinct signaling pathways. The plastids are considered as one of the main sources of ROS and under stress conditions or during plastid development, the production of ROS is enhanced leading to global changes in gene expression initiated to avoid irreversible damage to biomolecules. Although coping with ROS is a priority to avoid oxidative damage, it has become clear that modulation of ROS concentrations should not interfere with their functions as second messengers in stress signaling [88].

3.1.1. A cure for the *flu*

A specific function for $^1O_2$ in retrograde communication was discovered by the conditional fluorescent mutant, *flu,* of *Arabidopsis* [94]. FLU is a nuclear-encoded plastid membrane associated protein that acts as a negative regulator of the synthesis of δ-aminolevulinic acid (ALA) in the tetrapyrrole biosynthetic pathway. The *flu* mutant demonstrates an over-accumulation of protochlorophyllide (Pchlide)

in the dark, which when the mutant is transferred to light, produces an oxidative bust of $^1O_2$ (Fig. 2). The release of $^1O_2$ primarily activates genes encoding components involved in cell death and less than 15% of the $^1O_2$-responsive genes encode plastid proteins [95,96]. Thus, the $^1O_2$-mediated pathway may primarily be used for general stress responses rather than genome coordination. A similar $^1O_2$ burst, although at a much lower level, is produced by the P680 chlorophylls in the reaction centre of PSII when plants are exposed to excess light [97] (Fig. 2). Transcriptome analysis using the *flu* mutant and wild type plants treated with paraquat or methyl viologen (MV), which catalyses the monoelectronic photoreduction of O_2 to generate superoxide ($O_2^{\bullet -}$) and H_2O_2, demonstrated that $^1O_2$ activates a distinct set of genes that is different from those induced by superoxide, ($O_2^{\bullet -}$) and/or H_2O_2. In addition, it was demonstrated that H_2O_2 antagonizes the $^1O_2$-mediated stress responses observed in the *flu* mutant [98,99]. $^1O_2$ is very reactive and has a very short half-life (200 ns) [100,101] suggesting that the singlet oxygen derived plastid signal must exit the chloroplast in a different form. Possibly the singlet oxygen derived plastid signal includes second messengers such as compounds related to the oxidation of linonelic acid. This is supported by the high levels of the free hydroperoxides of linolenic acid (13-HOTE) observed in the *flu* mutant [102,103]. In addition, carotenoids are considered to be the main singlet oxygen quenchers in the plastids and it was recently demonstrated that light stress induces oxidation of β-carotene in Arabidopsis plants and consequent, accumulation of β-cyclocitral. This carotenoid derived compound was found to induce changes in expression of a large number of genes that have been identified as singlet oxygen responsive genes. Thus, β-cyclocitral represents another likely messenger involved in the singlet oxygen signaling pathway in plants [104].

EXECUTER1 and EXECUTER2 are two plastid-localized proteins identified through a screen for *flu* suppressor mutants. The *executer1/flu* double mutant over accumulates $^1O_2$ but abrogates the stress responses of the *flu* mutant [96]. However, inactivation of the EXECUTER1 gene in the *flu* mutant background is not sufficient to fully suppress $^1O_2$-induced changes in nuclear gene expression. Inactivation of both EXECUTER1/2 proteins in the *ex1/ex2/flu* triple mutant did provide full suppression of the $^1O_2$-induced genes suggesting that the singlet oxygen derived plastid signal

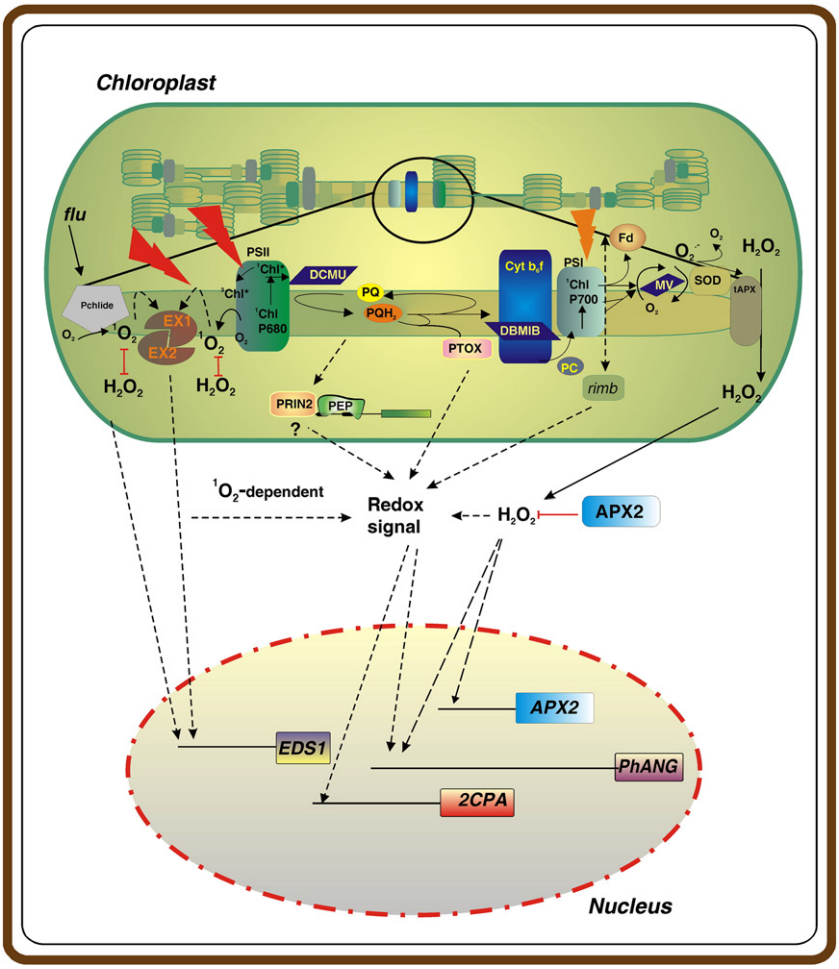

Fig. 2. Plastid signals related to photosynthetic electron transport activity. At least three different retrograde signals related to photosynthesis have been described 1) accumulation of $^1O_2$ 2) an exacerbated production of the $O_2^{\bullet -}$ and accumulation of its more stable product H_2O_2 3) an overreduced plastoquinone pool and/or a change in the redox status of the acceptor or donor side of PSI. Protochlorophyllide (Pchlide), accumulates in the *flu* mutant and produces an oxidative bust of $^1O_2$ when the mutant is transferred to light. A similar $^1O_2$ burst is produced by PSII following exposure to high light. EXECUTER 1 and 2 (EX1, EX2) have been identified as downstream components of the $^1O_2$ dependent signaling process regulating a large number of genes associated with cell death. A monoelectronic reduction of O_2 generates the radical superoxide ($O_2^{\bullet -}$), accumulation of this radical can also be induced by treatment with paraquat/methyl viologen (MV). $O_2^{\bullet -}$ is enzymatically converted to H_2O_2 by the superoxide dismutase (SOD). Ascorbate peroxidases are enzymes that detoxify H_2O_2 using ascorbate as a substrate. The thylakoid-anchored ascorbate peroxidase (tAPX) is involved in the breakdown of H_2O_2 to H_2O in plastids and cytosolic isoforms of APX (cAPX) control of the cytosolic H_2O_2 concentration. H_2O_2 regulates the expression of genes involved in plant development and stress responses with a particular strong influence on the expression of *APX2*. The redox state of the PETC is modified by the inhibitors DCMU and DBMIB and is correlated with changes in the expression of *PhANGs*. PTOX is a plastoquinol terminal oxidase and transfers electrons from the PQ pool to molecular oxygen and thereby modulates the redox status of PQ. PTOX is crucial during early chloroplast biogenesis when the electron transport chain is not yet fully assembled and functional. PRIN2 links redox regulation of *PhANGs* to the activity of the plastid encoded RNA polymerase (PEP). Redox imbalanced mutants (*rimb*) demonstrate a mis-regulation of cys-peroxiredoxin, 2CPA in response to the redox state of the PSI acceptor side.

requires concerted action of both EXECUTER1 and EXECUTER2 [105] (Fig. 2). Another suite of *flu* suppressor mutants named *soldat* (*s*inglet *o*xygen-*l*inked *d*eath *a*ctivator) were obtained in a second screen for mutants that abolished $^1O_2$-dependent cell death without affecting protochlorophyllide accumulation [106–109]. The described loci *SOLDAT8* and *SOLDAT10* were identified as the sigma factor 6 (SIG6) subunit of the plastid-encoded RNA polymerase (PEP) and a plastid-localized protein related to the human mitochondrial transcription termination factor mTERF, respectively. The phenotype of the *soldat8* mutant was explained by fact that the reduced transcription of chloroplast encoded photosynthesis genes induced a stress acclimation response giving rise to the suppression of cell death in the *flu* seedlings [108]. In *soldat10,* plastid-specific rRNA levels were decreased and protein synthesis in the plastids of *soldat10* was attenuated resulting in a suppression of cell death similar to that observed in *soldat8* [109]. Thus, the components described by the *soldat* mutants were general components essential for chloroplast function and not signaling components specifically involved in the $^1O_2$-triggered cell death response. Another screen designed to identify novel regulatory components of the $^1O_2$-responsive AAA-ATPase promoter was performed in the *flu* background transformed with the *LUCIFERASE* reporter gene under the control of the AAA-ATPase promoter (Baruah et al. [106]). A mutant with constitutively high luciferase activity ***c****onstitutive* ***a****ctivators of* ***A****AA-ATPase* was described (*caa*) that encoded PLEIOTROPIC RESPONSE LOCUS 1 (PRL1) [107]. This nuclear WD-repeat protein has been assigned a role in plant innate immunity response against pathogens and was identified as a component of the conserved proteolytic NTC/MAS complex together with CDC5 and MOS4 [110–112]. The same mis-regulation of AAA-ATPase was reported for mutants for each of the other components of the complex, indicated that the NTC/MAS complex, rather than PRL1 specifically, is responsible of the repression of AAA-ATPase expression [107].

Although the *flu* mutant allowed identification of some important players involved in plant cell death, the sudden and immense burst of $^1O_2$ observed in the *flu* mutant is distinct from what a plant experiences during physiological stress conditions. A more physiological stress condition to study $^1O_2$-induced signaling, without development of extensive cell death, was described by Alboresi and coworkers [113]. The experimental model used was the *npq1lut2* double mutant that lacks the quencher molecules lutein and zeaxanthin and shows a reduced ability to dissipate excess energy by NPQ. Following exposure to high light and low temperatures *npq1lut2* increased the production of $^1O_2$ compared to wild type. Furthermore, the site of $^1O_2$ accumulation was shown to be the reaction centre of PSII, validating the physiological relevance of this model in comparison to the *flu* mutant. When the gene expression profile in response to high light and low temperature was investigated in the *npq1lut2* double mutant, a smaller number of genes where differently expressed in *npq1lut2* compared to what was shown in the *flu* mutant [113]. Even so, the induction of genes encoding lipases, fatty acid desaturases associated with jasmonic acid (JA) production and *EX2* was shared between *npq1lut2* and the *flu* mutant indicating a similar response. For future studies, the *npq1lut2* mutant background in combination with a reporter gene under the control of a $^1O_2$-responsive promoter would be a promising system to screen for true signaling components of the $^1O_2$-pathway.

Cross-talk between H_2O_2- and $^1O_2$-dependent signaling pathways was suggested to contribute to the fine-tuning of the response to environmental stress [99]. Reduction of the plastidic pool of H_2O_2 by overexpression of a thylakoid-bound peroxidase enhanced the $^1O_2$-mediated response of cell death and growth arrest typically observed in the *flu* mutant. Comparative analysis of the transcriptomes in response to specific ROS also demonstrated that $^1O_2$ accumulation triggered changes to a particular set of genes and a specific cellular response that is, in part, antagonistic to the H_2O_2 response [98]. However, a possible physiological explanation for this could be that H_2O_2 is able to keep Q_A in an oxidized state and thereby favors electron movement from PSII, keeping the $^1O_2$ release from PSII low [97,99,114].

3.1.2. H_2O_2, a source of oxidative stress and a second messenger

Plastids are important sites of production of H_2O_2 [115] and the production and accumulation of H_2O_2 under normal cellular metabolism is correlated with a tight regulation of the complex network of scavenging mechanisms [116]. However, under stress conditions the equilibrium between production and scavenging of H_2O_2 is perturbed, resulting in a transient increase in H_2O_2 levels. Increases in foliar H_2O_2 concentrations have been shown to be important for the induction of the ascorbate peroxidase gene, *APX2*, and for the expression of a number of genes involved in plant development and stress responses [117,118] (Fig. 2).

The importance of H_2O_2 accumulation in signaling has been confirmed by the unexpected phenotypes of mutants with compromised levels of H_2O_2-scavenging enzymes [119]. These mutants demonstrated an increased tolerance to oxidative stress generated by a constitutive activation of an acclimation process triggered by the accumulation of H_2O_2. H_2O_2 is thought to move across biological membranes through aquaporins [120] and chloroplast-derived H_2O_2 could therefore directly influence the functions of cytosolic signaling components. The role for H_2O_2 as an intracellular signaling molecule was demonstrated by its local control of the expression of *APX2* in the response of plants exposed to excess light [89,121] and as an initial signal for the propagation of systemic responses to a wide range of stress conditions [121–123]. Studies of isolated thylakoid membranes and intact chloroplasts showed that even under low light conditions, part of the plastid-produced H_2O_2 reached the cytosol, supporting the importance of the H_2O_2 produced in the plastids in a wide array of stress responses [120,124].

The induction *APX2* expression is one of the most commonly used markers for the H_2O_2 response, and screens for mutants with altered expression of *APX2* have been performed. The *rax1-1* (*regulator of APX2 1-1*) mutant showed a constitutive expression of *cAPX2* similar to that observed in wild type plants following exposure to excess light or wounding [125]. The *rax1-1* was shown to have a mutation in the gene encoding *GLUTAMYLCYSTEINE SYNTHETASE 1* (GSH1), which is the enzyme that catalyses the key regulatory step in the biosynthesis of glutathione, a major cellular antioxidant and ROS scavenger [126]. Two other alleles of this mutant, *cad2-1* and *rml1* were described previously [127,128]. The *rax1-1* mutant suggested that there is a link between the levels of glutathione and the expression of other components of the plant antioxidant defense such as *APX2* [125]. Analysis of the expression profile of *rax1-1* when grown under normal growth conditions also showed an induction of the genes encoding the stromal enzymes of the ascorbate cycle and ferritin. No increase in the levels of H_2O_2 could be detected in *rax1-1* compared to wild type, suggesting a more complex regulation of *APX2*. Possibly modifications of thiol groups independent of ROS or increased levels of the signaling metabolite PAP (see previous section) could be involved in the regulation of *APX2* expression. Crosstalk between GSH and H_2O_2 has been suggested by overlapping gene expression profiles of plants with increased levels of H_2O_2 (catalase *cat2* mutant) and oxidized glutathione (GSSG) (glutathione reductase 1 *gr1* mutant), respectively [129–131].

Although the importance of the control and modulation of the cytosolic H_2O_2 content is clear, we have just started to discover that the source of the H_2O_2 signal can determine the cellular response. There is an increasing number of reports suggesting that it is necessary for the plant to perceive the signature of the ROS signal to trigger the correct change in gene expression. In other words, there is an unknown mechanism by which the plant cell can recognize the origin of a specific ROS signal and trigger the appropriate response [132]. Microarray data from mutants impaired in different antioxidant enzymes such as catalase, Cu/ZnSOD, APX1 and AOX were compared to

determine the genetic responses to ROS signals originating in the peroxisomes, plastids, cytosol and mitochondria, respectively [98]. In this microarray-based study the selectivity and specificity of ROS signaling was demonstrated by distinctive transcriptome profiles generated by ROS signals of different origins [98]. Evidence for cross-talk between ROS of different origin was provided by the role of the apoplastic ROS-producing enzyme NADPH oxidase RbohD in ROS signaling during pathogen response [133]. The Arabidopsis Enhanced Disease Susceptibility1 (EDS1) regulates defense and cell death against biotrophic pathogens and controls cell death propagation in response to chloroplast-derived ROS [134,135]. Chloroplastic ROS signals are processed by EDS1 to produce counter-balancing activities of salicylic acid (SA) and RbohD in the control of cell death. Hence, the ROS signal generated by photooxidative stress will initiate two opposite reactions; onset of the cell death program or an acclimation response, depending on the origin and strength of the signal. While RbohD triggers an oxidative burst of H_2O_2 from the apoplast linked to the start of the cell death program, EDS1 antagonizes this reaction by promoting accumulation of H_2O_2 in the plastid [134]. These results emphasize the need to identify the production sites of ROS more precisely [136].

3.2. Signals triggered by the redox state of components in the photosynthetic electron transport chain

A coordinated response of photosynthesis related genes encoded both in the nucleus and the chloroplast is essential both under biogenic or operational conditions. Photosynthetic electron transport is central to this coordination of gene expression. Thus, the first steps of energy metabolism in the plant are at the same time sensors controlling photosynthetic activity. The lack of well-characterized components identified from mutants has left the field in debate over whether the actual site of sensing and control is in the photosynthetic electron transport chain (PETC), the redox state of specific stromal component(s) and/or the metabolic status of the chloroplasts [137]. However, recent reports indicate a strong correlation between the redox status of PETC and regulation of gene expression in both the nucleus and the chloroplast [138–140].

3.2.1. The redox state of the PQ pool

The first report that demonstrated a connection between the redox state of the plastoquinone (PQ) pool and expression of nuclear encoded photosynthesis genes came from pioneering studies with the algae *Dunaliella tertiolecta* [141]. The redox state of the PQ pool was modified by two different inhibitors of photosynthetic electron transfer; 3-(3,4-dichlorophenyl)-1,1-dimethylurea (DCMU) and 2,5-dibromo-3-methyl-6-isopropyl-benzoquinone (DBMIB). DCMU blocks the flow of electrons from PSII to PQ leaving PQ oxidized, and DBMIB inhibits electron transfer from PQ to the cytochrome b_6f complex resulting in a more reduced PQ pool [141]. In this elegant piece of work, it was put forward that these inhibitors generated antagonistic signals leading to an increase (DCMU) or decrease (DBMIB) of *LHCB* expression. A model was proposed where the redox state of PQ was sensed in order to modulate the capacity to harvest and funnel light energy into the reaction centre of PSII (Fig. 2). Similar acclimatory responses were observed also in *Dunaliella salina* and *Chlorella vulgaris* when exposed to low temperature under moderate light intensities to mimic high light conditions, suggesting that the mechanisms of photosynthetic adjustment are regulated by the redox poise of intersystem electron transport as reflected by changes in excitation pressure [142–144]. The redox state of PQ was later shown to be correlated with the expression of photosynthetic genes encoded also in the chloroplast [145–147]. In isolated chloroplasts it was demonstrated by run on transcriptional assays that the ratio between PSII/PSI, determined by the expression of the plastid encoded genes *psaA/B* and *psbA,* was controlled by light specifically absorbed by either PSII or PSI [146]. Thus, similar to what was previously observed in *Dunaliella tertiolecta*, the expression of the plastid encoded genes *psaAB* and *psbA* was responding to the redox state of the PQ pool.

However, subsequent detailed analysis of cyanobacteria and higher plants using the same inhibitors of electron transport and wavelengths that preferentially excited either PSII or PSI, demonstrated that the redox state of the PQ pool was not the major source of the high-light mediated plastid signal [148–150]. Light shift experiments, combined with DCMU, demonstrated that only 54 Arabidopsis genes were “ideal redox regulated genes” or regulated directly by the reduction state of PQ [148]. Among those 54 genes, only 2 genes encoded components directly associated with photosynthesis. In these experiments Arabidopsis plants at the six-leaf stage were acclimated to specific PSII or PSI light, the plants were then shifted to the other light quality to produce a reduced (PSI-light to PSII-light) or oxidized (PSII-light to PSI-light) redox signal. A few years later the same group performed time course experiments to study the role of the redox state of the PQ pool using microarrays and metabolic profiling [138]. These experiments demonstrated that the reductive redox signal has a faster kinetics (30 min) than the oxidative signal (2 hr). Furthermore, the two responses and their effects on the transcriptome and metabolome were not complementary, suggesting that two different pathways are involved in communicating the redox state of the PETC. In response to a reduction signal, *PhANG* expression demonstrated a clear repression after 2 h, but after only 8 h the repression was diminished [138]. Several functional groups were represented among the early redox responsive genes, including transcription factors and protein modification factors, whereas the genes responding somewhat later to the redox changes were genes encoding components involved in energy distribution [138]. Taken together, these results suggest that in addition to that the redox state of PQ is an important part of retrograde signaling there is a much more complex signaling mechanism rather than the simple switch between oxidized and reduced PQ pool [138]. Another important conclusion from the kinetic experiments is that the observed impact on nuclear gene expression depends not only on the signaling system that is activated but also on the time point of observation [138]. This is analogous to the observed discrepancies in the responses from the tetrapyrrole mediated signaling (See previous section). Taken together, this argues for further detailed kinetic analyses of gene expression responses under different environmental conditions.

Elements on the reducing side of PSI have also been shown to be important in light regulated modulation of nuclear gene expression [150]. In addition, the CO_2-fixation rate was demonstrated to influence the expression of nuclear encoded photosynthesis related genes, suggesting that the metabolic activity of the chloroplast could also be a source of plastid signals [150]. This suggests that rather than the reduction state of the PQ itself, the generation of metabolites or signaling molecules during photosynthesis could be involved in the relay of information from chloroplasts to the nucleus. The first true *r*edox *imb*alanced mutants described were the *rimb* mutants [151] (Fig. 2). In the *rimb* mutants, the expression of the nuclear gene encoding the antioxidant enzyme 2-cys-peroxiredoxin, 2-CPA, is uncoupled from the redox state of the PSI acceptor side. It was also reported that this part of PSI might emit a signal to control the expression of Ferredoxin isoform under conditions with reduced availability of oxidized electron acceptors (also known as acceptor side limitation) [152]. Cloning of the *RIMB* genes could provide a breakthrough in our understanding of the redox-mediated retrograde signaling pathway(s).

So far most of the emphasis regarding the redox-mediated signal has been associated with responses to changes in the environment or so called operational control. However, there are also reports where an imbalance of photosynthetic electron transport is perceived in the frame of biogenic control, or in other words, during the initial stages of plastid development. The signals linked to PQ and the

redox state communicate the functional state of the plastids and are capable of stopping the plastid developmental process at different stages. This is shown in the responses of the albino mutant pds3 and the variegated mutant, *immutans*. The pds3 knockout mutant lacks phytoene desaturase (PDS) and consequently has impaired synthesis of carotenoids. This defect results in an albino phenotype due to chloroplast photooxidation [139]. IMMUTANS (IM) or PTOX functions as a versatile plastoquinol terminal oxidase in plastid membranes, where it transfers electrons from the PQ pool to molecular oxygen. IM is a component of a redox pathway that desaturates phytoene where electrons are transferred from phytoene to PQ via PDS, and from PQ to oxygen via IM [153] (Fig. 2). Initially, IM was described as safety valve, similar to the mitochondrial terminal oxidase AOX, to keep the PQ pool oxidized [154] but IM also influences plastid biogenesis by modulating excitation pressure of PSII [155–157]. As demonstrated by the immutants phenotype, the role of IM is crucial during early chloroplast biogenesis when the electron transport chain is not yet fully assembled and functional. A recent model suggested that the redox state of the PQ pool acts as a rheostat of excitation pressure-mediated retrograde signaling during chloroplast development and is a determinant of the suite of genes that is expressed during chloroplast biogenesis [139]. Whether the rheostat is set high (as in pds3), intermediate (as in im) or low (as in WT) is a crucial determinant for chloroplast biogenesis [139].

3.2.2. A link between PEP activity and redox regulation of PhANG expression

Plastid gene expression (PGE) is essential for the initiation of *PhANG* expression. Inhibitors of plastid transcription and translation block the induction of genes encoding light-harvesting complex apoproteins (LHC) and the small subunit of Rubisco (RBCS) [14,40,158]. Impaired PGE is mediated to the nucleus by GUN1, a chloroplast localized pentatricopeptide-repeat (PPR) containing protein with unknown function [21]. PGE is also under tight redox control [159] and it has been suggested that redox signals from the thylakoid membrane control plastid gene expression via complex networks of phosphorylation events [160]. Phosphorylation of sigma factors, as well as phosphorylation of the plastid encoded RNA polymerase (PEP) itself, has been shown to regulate plastid gene expression [161,162]. Comparatives studies of the sequences of the different sigma factors and complementation studies performed on SIG6-KO plants have shown that reversible phosphorylation of sigma factors influences PGE activity *in vivo* [163]. Furthermore, SIG6 was shown to be a substrate of the plastid transcription kinase cpCK2 (PTK/cpCK2) [163,164]. Complementary studies indicated that the role of SIG1 in PGE is also regulated by its phosphorylation state and in this case, the sensor kinase CSK has been suggested to link photosynthetic activity to SIG1 phosphorylation and expression of photosynthesis genes in the chloroplasts [165]. Another kinase suggested to be implicated in PGE is the thylakoid protein kinase STN7 required for state transitions and photosynthetic acclimation [166,167]. STN7 has been suggested to participate in the implementation of the redox signal from the chloroplast to the nucleus [167], however, recent microarray analyses revealed that even though over 300 genes were expressed differently in the *stn7* mutant compared to wild type there were no statistically significant differences in the levels of transcripts of photosynthesis genes between *stn7* and wild type. Thus, STN7 kinase activity as such does not directly affect the transcription of *PhANGs* in Arabidopsis [168,169].

Isolations of plastid transcriptionally active chromosomes (TAC) have revealed that in addition to the core components of PEP, a large number of other proteins are required for chloroplast transcription. As many as forty to sixty proteins appear to be present in the TAC from chloroplasts [170] suggesting that regulation of plastid gene expression is both complex and sophisticated. The thioredoxin z (TRXz) was identified as a component of the TAC in the plastids [170]. The *trxz* mutant demonstrated suppressed expression of PEP dependent genes and the redox state of TRXz was proposed to regulate the kinases that, in turn, regulate PEP activity during dark-to-light transitions [171]. In a recent report also the redox regulation of nuclear encoded photosynthesis genes was linked to the activity of PEP, suggesting that components associated with the PEP complex respond to photosynthetic electron transport and generate a retrograde signal to regulate expression of nuclear encoded photosynthesis genes [140]. The novel component PLASTID REDOX INSENSITIVE2 (PRIN2) was isolated from a screen for mutants with impaired regulation of *PhANG* expression following exposure to excess light. The *prin2* alleles demonstrated a mis-regulation of *LHCB1.1* and *LHCB2.4* in response to excess light and inhibition of photosynthetic electron transport using the inhibitors DCMU and DBMIB. Plastid transcriptome analyses demonstrated that PRIN2 is required for full expression of genes transcribed by PEP [140]. Similar to the *prin2* mutants, the *ys1* mutant with impaired PEP activity [172] also demonstrated a mis-regulation of *LHCB1.1* and *LHCB2.4* expression in response to excess light, suggesting that a fully functional PEP complex is important for correct *LHCB* expression in response to redox changes to photosynthetic electron transport [140]. Possibly the PEP complex generates a retrograde signal enabling the plant to synchronize the expression of photosynthetic genes from both the nuclear and plastidic genomes (Fig. 2). Describing the exact mechanism by which the redox signal(s) is mediated to the nucleus is a challenging and exciting task for future research.

4. Proteins moving from the chloroplast to the nucleus, potential carriers of chloroplast signals

A major breakthrough was recently published describing a mechanism by which chloroplast signals are transduced to the nucleus. PTM, a transcription factor associated with the chloroplast envelope membrane, was shown to mediate chloroplast signals regulating *PhANG* expression [173]. Membrane-bound transcription factors (MTFs) have been shown to mediate diverse cellular functions through an intriguing regulated proteolytic activation mechanism [174]. The PTM protein has a DNA-binding homeobox domain, a different transcription factors (DDT) domain and a plant homeodomain (PHD) in its N-terminal and four transmembrane domains in the C-terminal [173]. Immunoblot analysis revealed that the full-length PTM was exclusively detected in the chloroplast outer envelope membrane. In addition, one band with a molecular weight of ~58 kDa, corresponding to the N-terminal fragment without the transmembrane domains, was detected in the nuclear fraction. Treatments with norflurazon and inhibitors of plastid protein synthesis such as lincomycin, and exposure to high light, increased the detection of the ~58 kDa band in the nuclear fraction. PTM processing and detection of the ~58 kDa band was dramatically suppressed by the serine protease inhibitor pefabloc, indicating that PTM can be processed by proteases in the chloroplast envelope and released to the nucleus upon signals triggered by stress [173].

The *ptm* mutant seedlings showed a gun phenotype similar to the *gun1* and *abi4* mutants when treated with norflurazon and lincomycin. Following exposure to high light, the *ptm* mutant also maintained expression of *LHCB*, in contrast to wild type where *LHCB* expression was significantly suppressed [173]. Thus, similar to GUN1 and ABI4, it appears as if PTM has a role in mediating multiple chloroplast-derived signals. The AP2-type transcription factor ABI4 was found to bind in close proximity of the CUF1 element of the *LHCB* promoter, preventing the binding of G-box-binding factors required for light-induced expression of *PhANGs* [21]. Analysis of the *gun1ptm* and *abi4ptm* double mutants suggested that PTM, GUN1 and ABI4 all act in the same signaling pathway. Furthermore, it was demonstrated that the *gun1* phenotype was suppressed by constitutive expression of the N-terminal fragment of PTM (N-PTM). Analysis of the *gun1* mutant also revealed that the level

of processed N-PTM was lower during stress compared to wild type, suggesting that GUN1 is important for PTM processing (Fig. 1).

ABI4 expression was reduced in the *ptm* mutant. The expression level of *ABI4* increased 14-fold in wild type seedlings following exposure to high light. However, in the presence of the protease inhibitor pefabloc, the increase was only 4-fold suggesting a link between the release of the N-PTM and stress induced induction of *ABI4* expression. Chromatin immunoprecipitation (ChIP) assay demonstrated that the PHD domain of PTM binds to the promoter region of *ABI4* and PTM was able to pull-down methylated histones, H3K4me3. H3K4me3 increased in the *ABI4* promoter when plants were treated with norflurazon, lincomycin or exposed to high light [173]. Thus, the PTM mediated activation of *ABI4* expression, necessary for the suppression of *LHCB* in response to retrograde signals, is associated with histone modifications [173]. It is clear that the chloroplast envelope membrane-bound transcription factor PTM plays a critical role in mediating stress related signals from the chloroplasts to the nucleus. Intriguingly, transgenic plants over-expressing the processed N-terminal fragment of PTM did not induce a retrograde response in the absence of inhibitors or stress suggesting that the regulatory network involved is complex and that additional stress signals are required to trigger changes in nuclear gene expression. Future analysis will hopefully reveal how PTM senses retrograde signals and what pathways, e.g. the tetrapyrrole mediated and/or the PEP dependent redox pathway, depend upon PTM for communication with the nucleus. In addition determining which protease(s) is involved in the processing of PTM and how this protease is regulated within the chloroplast will be of great interest to our understanding of retrograde signaling.

Another protein that has been proposed to move from the chloroplast to the nucleus is the Whirly1 protein and a possible retrograde transfer of Wirly1 was suggested [175]. The Whirly proteins were identified as transcriptional activators (PBF-2) involved in the induction of the pathogenesis-related nuclear gene *PR-10a* [176–178]. The Whirly1 protein was shown to be dually located in chloroplasts and nucleus of the same cell and the proteins were demonstrated to have the same size both in chloroplasts and the nucleus. However, the movement of Whirly1 from the chloroplast to the nucleus was demonstrated by inserting a construct encoding a HA-Whirly1 fusion protein into the plastid genome of tobacco and although the tagged protein was synthesized in the plastids, it was detected in the nucleus of the transplastomic tobacco line [175]. In addition, the transplastomic plants showed an enhanced expression of Whirly1-regulated PR genes under normal growth conditions without pathogen treatment. However, it is still elusive if a pathogen infection could trigger the retrograde movement of this transcription modulator to the nucleus or if the wild type version of the Whirly1 protein moves between the chloroplast and the nucleus. Whirly1 is nevertheless a very interesting candidate for transducing information from the plastid, where it functions primarily in RNA metabolism [179] to the nucleus where it modulates transcription of stress responsive genes.

5. Concluding remarks

The field of plastid-to-nucleus signaling has been very dynamic over the last few years and, as discussed in this review, there have been several major breakthroughs leading to a much more advanced understanding of the mechanisms involved in the communication between the plastids and the nucleus. The main debate has been whether there was a true "plastid factor" or if there were simply metabolite signatures giving rise to changes in nuclear gene expression [137]. This debate has stimulated a number of different researchers in the field to use novel approaches and different experimental models. These recent findings, as highlighted in this review, have made it clear that there are several plastid factors, including tetrapyrroles, phosphonucleotides and peptides and that these play important and distinct roles in cellular processes ranging from coordination of cell cycle and coupling of DNA replication to suppression of *LHCB* associated with histone modifications.

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